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14. ABSTRACT Lung cancer has the highest mortality rate of all cancers in the United States and has adversely affected the lives of many Americans. Typically, only 16% of patients survive 5 years beyond initial diagnosis. The goal of this proposal is to try to improve application of a drug, dasatinib, which has some promise for lung cancer treatment. Dasatinib is a targeted drug, with action that involves blocking the function of a group of proteins (defined as the Src group) whose action is important in lung cancer metastasis. In our study, we have been testing whether the action of dasatinib in lung cancer is enhanced by combining it with a second agent, ganetespib, that targets Src and other pro-cancerous proteins by an alternative mechanism. We have also been evaluating whether cellular status of a protein, NEDD9, that we have shown to bind directly to Src, influences the activity of dasatinib. Using in vivo analysis, experiments in progress are indicating that mice lacking NEDD9 are greatly sensitized to dasatinib but not ganetespib, and that mice lacking NEDD9 develop more aggressive lung cancers than those with intact NEDD9; while the dasatinib/ganetespib combination does not improve the efficacy of dasatinib.					
15. SUBJECT TERMS Nedd9, Src, HSP90, ganetespib, dasatinib, KRAS, NSCLC					
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INTRODUCTION: Elevated activity of SRC family kinases (SFKs) and heat shock protein (HSP) 90 are both associated with cancer progression, invasion, tumor angiogenesis and drug-resistance, and both are targets of inhibitors currently in clinical development for the treatment of several cancers, including lung cancer. The scaffolding protein NEDD9 binds SFKs and controls their activity, and has very recently been defined as a factor regulating drug response and prognosis in lung cancer. The first evaluation of the efficacy of dual inhibition of SFKs and HSP90 lung cancer in the context of NEDD9 expression will be performed. The objectives of the proposal are to 1) Explore the therapeutic potential of combining dasatinib with ganetespib in lung cancer; 2) establish whether NEDD9 expression regulates response to dasatinib and ganetespib combination; and 3) define relevant related biomarkers for use in clinical assessment of response to the combination.

KEYWORDS: *Nedd9, Src, HSP90, ganetespib, dasatinib, KRAS, NSCLC.*

ACCOMPLISHMENTS:

What were the major goals of the project?

Major Task 1 – Multiple different lung cancer cell lines will be used to test the therapeutic potential of combining dasatinib with ganetespib in the context of different NEDD9 expression levels.

Major Task 2 – Utilize an *in vivo* lung cancer model to investigate the efficacy of combining dasatinib and ganetespib in the presence or absence of NEDD9.

Reverse phase protein array (RPPA) will be performed to identify relevant signaling biomarkers.

What was accomplished under these goals?

Because of the anticipated longer period of analysis, we first began with performance of Major Task 2, assessing the effect of NEDD9 genotype with dasatinib and/or ganetespib treatment for effects on tumor growth. Accrual of cohorts was initially slowed because of slow breeding of mice required to generate the requisite genotypes. However, by 2016, this was performed completely as described in the Statement of Work, and is now completed. We first induced tumor formation in 129S/Sv-*Kras*^{tm3Tyj/J};Nedd9^{+/+} mice and 129S/Sv-*Kras*^{tm3Tyj/J};Nedd9^{-/-} mice via inhalation of Adeno-Cre, followed by

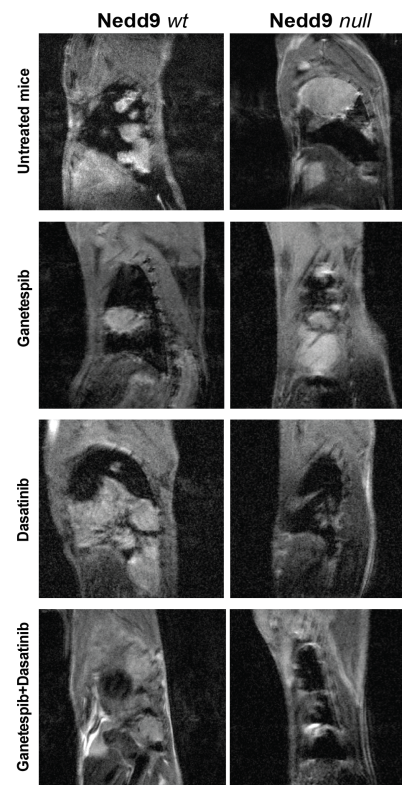


Figure 1. Representative MRI images from Nedd9wt or Nedd9 null *Kras* mutant mice, treated with noted drugs.

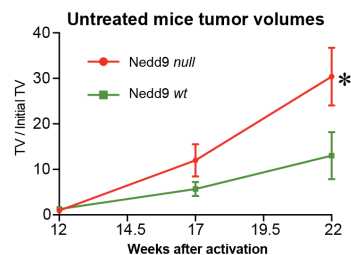


Figure 2. Tumor volume (TV) differences over time associated with Nedd9 genotype. *, $p < 0.05$

MRI imaging at regular intervals to detect tumor initiation and growth, followed by euthanasia and processing of tissues for mechanistic analysis. For dosing with dasatinib and ganetespib, this began at 12 weeks after activation, and proceeded through the experimental endpoint. 10 mice were used per time point. Representative MRI data describing tumor volume (TV) are shown in Figure 1. Quantification of data is shown in Figure 2 and 3. Based on the comparison of mice treated with vehicle, dasatinib, ganetespib, and the combination of ganetespib and dasatinib, we were able to make several conclusions.

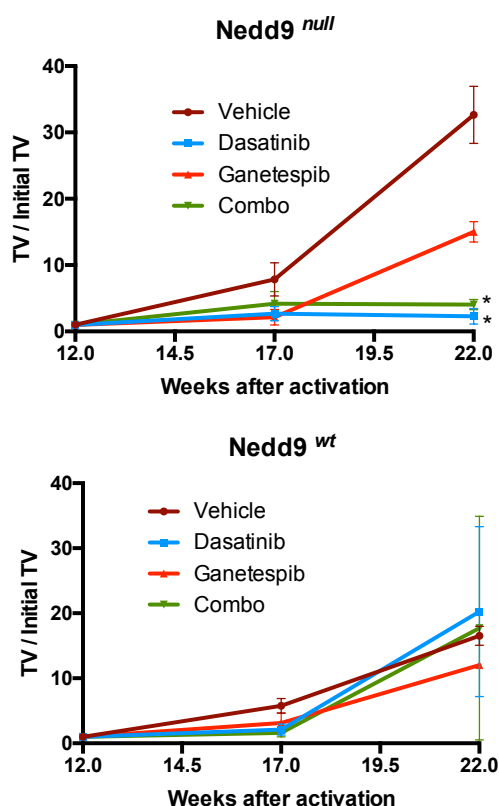


Figure 3. Quantitation of results from MRI analysis showing growth in Kras-dependent lung tumors, and in the context of a Nedd9 null or a Nedd9 wt genotype, following treatment with the indicated drugs. *, $p < 0.05$.

These confirmed and extended the results of the MRI imaging, demonstrating that absence of NEDD9 sensitized tumors to dasatinib: quite surprisingly, dasatinib-treated tumors grew more aggressively than tumors treated with vehicle. We also observed that development of tumors in the absence of NEDD9 significantly exacerbated the tumor phenotype. We also note, this exacerbation was in fact more severe than indicated by

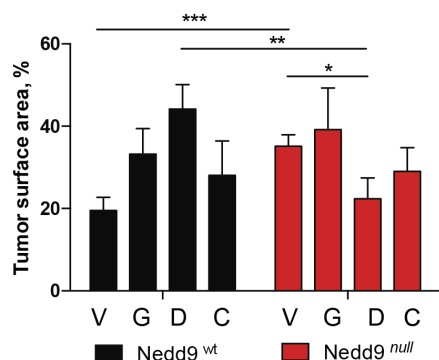


Figure 5. Quantitative assessment by Vectra of area of Kras-dependent lung tumors with Nedd9 null or Nedd9 wt genotypes, treated with the indicated drugs. *, $p < 0.05$, V, vehicle, G, ganetespib, D, dasatinib, C, combination.

First, we detected a robust effect of NEDD9 genotype on response to dasatinib, and on tumor growth in untreated mice. Unexpectedly, this reflected an increased rate of tumor growth in tumors lacking NEDD9 ($p < 0.05$), contrasting with previous publications that have suggested depletion of NEDD9 in lung cancer models, using siRNA or shRNA, results in reduced tumor growth (1, 2). Second, we found that tumors lacking NEDD9 had a much-heightened response to dasatinib ($p < 0.05$). We did not detect an effect of NEDD9 genotype on response to ganetespib, nor did we detect improved tumor control with the ganetespib/dasatinib combination over the response seen with dasatinib alone, regardless of NEDD9 genotype.

At the end of experiments, lungs and adjacent tissue were excised and formalin-fixed and paraffin embedded (FFPE) and some tumors excised and used to prepare protein lysates for analysis by RPPA analysis or Western blotting. Hematoxylin and eosin (H&E) staining was performed on all FFPE tissue from tumors. Representative images for results are shown in Figure 4. Quantitation of this data is shown in Figure 5.

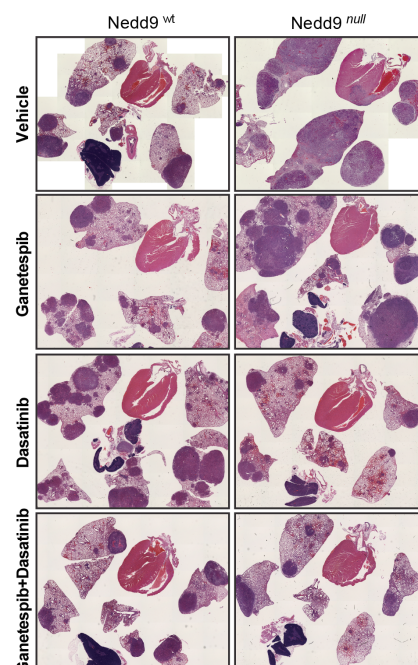


Figure 4. Representative H&E staining showing Kras-dependent lung tumors, with Nedd9 null or a Nedd9 wt genotype, and treated with the indicated drugs.

average values indicated in the graph, because a number of the NEDD9-null, vehicle-treated mice needed to be euthanized before the experimental endpoint, due to humane criteria (detection of respiratory distress due to rapidly growing tumors), which meant that some of the most aggressive phenotypes are missing from the analysis.

We have been analyzing the tissue specimens with multiple markers relevant to tumor growth, apoptosis, and SRC-family signaling. These include Ki-67, caspase cleavage, ERK phosphorylation, and epithelial-mesenchymal transition (with markers including the protein vimentin, associated with mesenchymal cells), with consultation from a pathologist. We also are working on performing CD31 analysis, but have not as yet optimized antibody conditions for IHC, due to issues with background. Representative data is shown in Figures 6 and 7.

Focusing on the NEDD9 genotype analysis, tumors developing in the context of a NEDD9-null genotype have increased Ki-67 index, and increases in phospho-ERK expression, both indicative of a higher rate of proliferation. This is supported by an increase in average tumor area of mice

euthanized at similar time points (36% versus 19% of total lung area/section; $p < 0.001$), versus a decrease in separable total tumor numbers (10 versus 15/section; $p < 0.01$), indicating larger tumors have merged together. They have no evident changes in levels of caspase-3 expression, which is low in all cases (not shown).

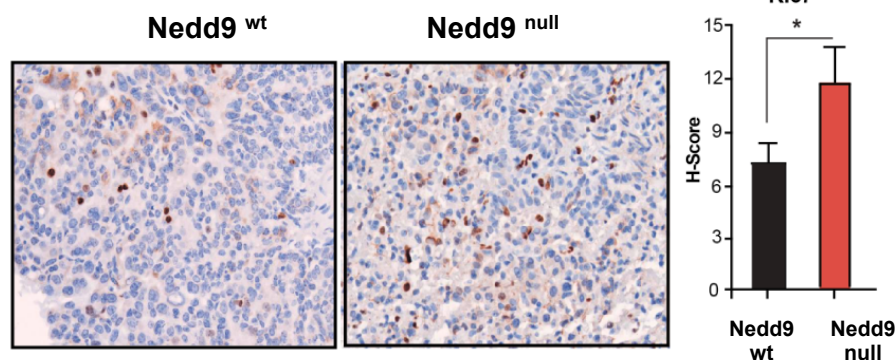


Figure 6. Quantitative assessment by Vectra of Ki-67 expression in Kras-dependent lung tumors with Nedd9 null or Nedd9 wt genotypes. *, $p < 0.05$.

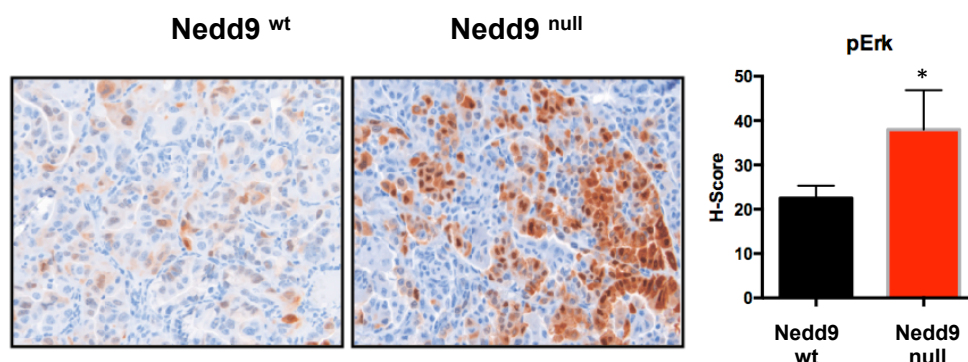


Figure 7. Quantitative assessment by Vectra of phosphorylated ERK1/2 (pErk) expression in Kras-dependent lung tumors with Nedd9 null or Nedd9 wt genotypes. *, $p < 0.05$.

Strikingly, tumors with a NEDD9-null genotype have the tendency to invade neighboring heart tissue, which was observed in almost 50% of NEDD9-null cases, but none of the tumors with intact NEDD9 (Figure 8). Compatible with this, NEDD9-null tumors had a very significantly increased proportion of cells staining positively for vimentin (Figure 9).

By one interpretation, this is compatible with an interpretation of greater EMT and migration. However, the morphology of the cells is somewhat unusual (large, rounded); it is possible that this represents transition to an amoeboid, rather than mesenchymal, phenotype, as Nedd9 has been proposed to be necessary for EMT transitions (3). We are

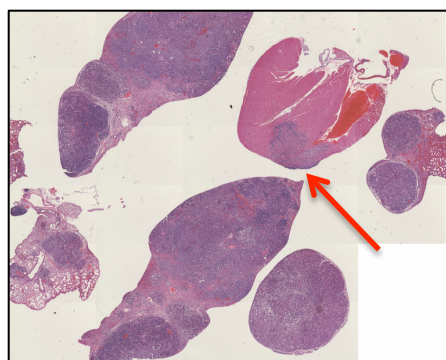


Figure 8. Arrow indicates Kras lung tumor with a Nedd9-null genotype invasion into heart tissue.

currently performing Vectra-based quantitative analysis of the complete set of data for the study (which takes time for scanning slides and analysis, plus the need to schedule time on the machine versus other institutional users), and the complete dataset will be included in resulting publications. Qualitatively, and as expected based on the MRI results and our hypothesis, we observe that dasatinib treatment reverses the invasiveness to heart of NEDD9-overexpressing tumors, and selectively reduces hallmarks of cell proliferation in while ganetespib does not discriminate, but reduces these features in tumors with and without NEDD9.

Tumors were dissected and sent to the core facility at MD Anderson for reverse phase protein array (RPPA) analysis. A partial set of data represented as heatmaps is shown in Figure 10 (these are quite large datasets, limiting the ability to display *in toto*). A subset of data, using heatmap to represent significant changes associated specifically with the NEDD9 genotype, is shown in Figure 11: all data shown in this representation are statistically significant, seen across multiple independent tumors collected from individual animals. This analysis leads to some interesting conclusions. For example, NEDD9 depletion causes a reduction in levels of active and total Src kinase (the target of dasatinib, and NEDD9 functional partner). This offers a ready explanation for why these tumors would be sensitized to dasatinib – i.e., levels of Src are already depressed, so

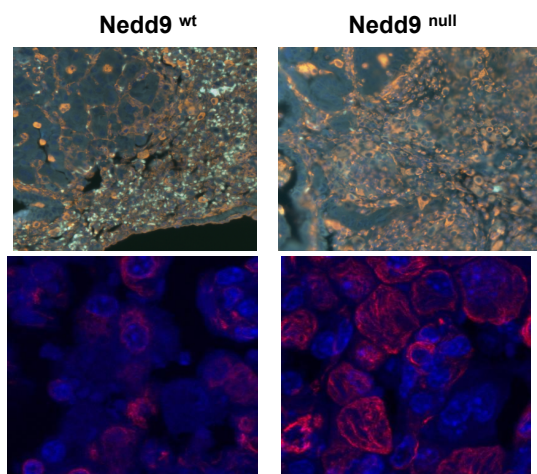


Figure 9. Visualization of Kras lung tumors with indicated Nedd9, stained to visualize vimentin. Top, 40X images on Vectra (orange signal is vimentin). Bottom, 180X images on Leica (red; with DNA counterstained with DAPI, blue).

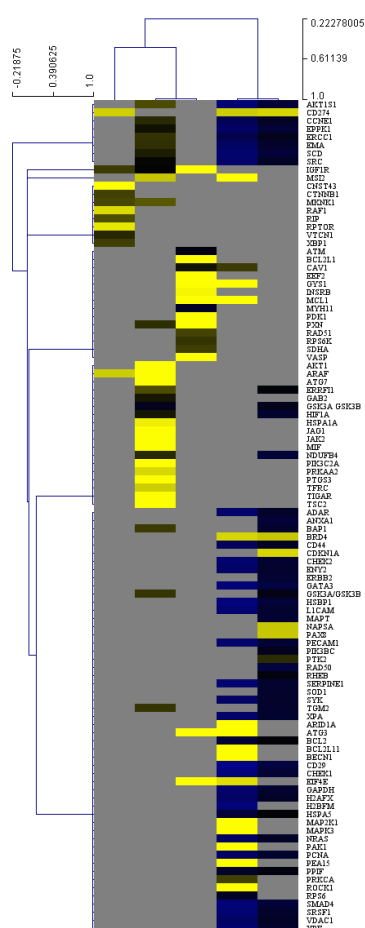


Figure 10. RPPA clusters among treatment/genotype groups, representative data. Yellow, elevated expression; blue, reduced expression.

was performed on day 0, and at 24 hours, drug was applied at 8 different concentrations, ranging from 1 pM through 100 μ M (Figure 13). After an additional 72 hours, CellTiterBlue was used to measure cell viability.

lower levels of dasatinib are sufficient to entirely eliminate Src-dependent functions. However, as with the paradoxical increase in growth of Nedd9-deficient tumors, it is very surprising, as the Nedd9-deficient tumors are more invasive in vivo – a phenotype that typically requires active Src.

One possibility is that NEDD9 deficiency is causing cells to undergo mesenchymal-amoeboid transition, which would perhaps be compatible with the phenotype of large cells that we see in the IHC analysis. We are investigating this possibility, which extends beyond the scope of this application: however, the fact that levels of ROCK1 are detectably altered in the RPPA analysis is suggestive, as changes in ROCK1 activity are implicated in amoeboid transitions. Another extremely interesting set of observations is the fact that absence of NEDD9 triggers the elevated expression of some proteins associated with autophagy (BECN1, ATG3, etc.): this process in some cases has been shown to be tumor promoting and to affect drug response, but to date, it

has never been linked to changes in NEDD9 activity. This also is being investigated. We will specifically look for changes in expression of proteins related to autophagy and amoeboid migration as we complete analysis of data for ganetespib and dasatinib treatment.

For Major Task 1, we performed analysis for 3 cell lines, with qualitatively similar results in all cell lines, although with some differences. We also performed preliminary tests evaluating several other proposed cell lines, but in this analysis, we were unable to detect NEDD9 at the mRNA or protein level, confounding further use of these models in the experiments. We focused on the three models with clearly detectable NEDD9. For this analysis, lung cancer cell lines were transfected with siNEDD9 or siControl (Figure 12). Western analysis was routinely performed to confirm effective knockdown of NEDD9 (typically by >75-80%). This analysis confirmed that NEDD9 depletion resulted in reduction in Src activity (Y416 SRC), and AKT activity (T308 AKT), similar to the profile seen in tumor tissue. In contrast, knockdown of NEDD9 led to a slight increase in the activation of ERK1/2 kinase, which varied depending on what cell line was analyzed.

For assessment of drug response, experiments were performed in triplicate wells in a 96 well plate, with cells treated with vehicle, ganetespib, dasatinib or dasatinib plus ganetespib. In a typical experimental design, siRNA depletion

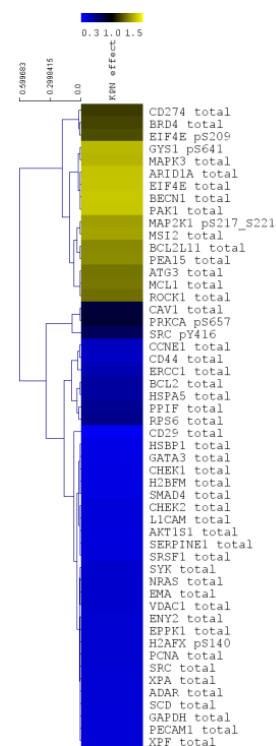


Figure 11. Proteins significantly ($p < 0.05$) elevated (yellow) or decreased (blue) as predicted by RPPA for multiple Nedd9-null versus Nedd9-wt dissected lung tumors.

Figures 13 and 14 show representative data, averaged across multiple experiments. All data in the presented graph are normalized to SCR or NEDD9 siRNA depleted cells, treated with vehicle.

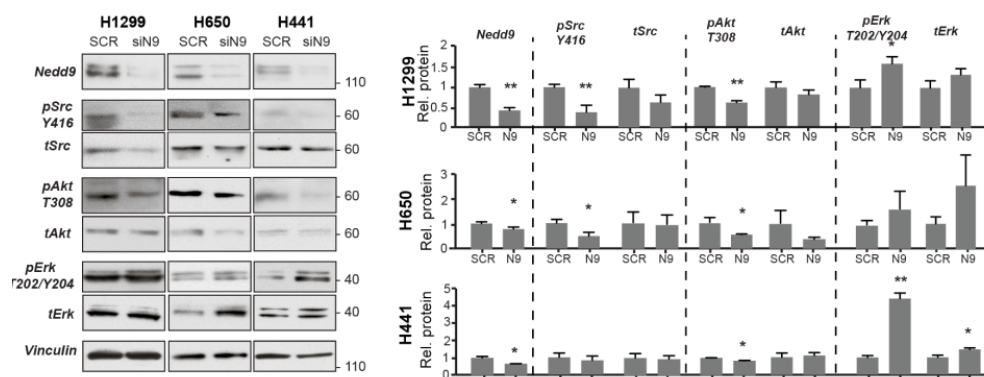


Figure 12. Representative Western blot data and quantitation from multiple independent experiments of the consequence of Nedd9 depletion (siN9) for expression and activation of the indicated signaling proteins. *, $p < 0.05$, **, $p < 0.01$.

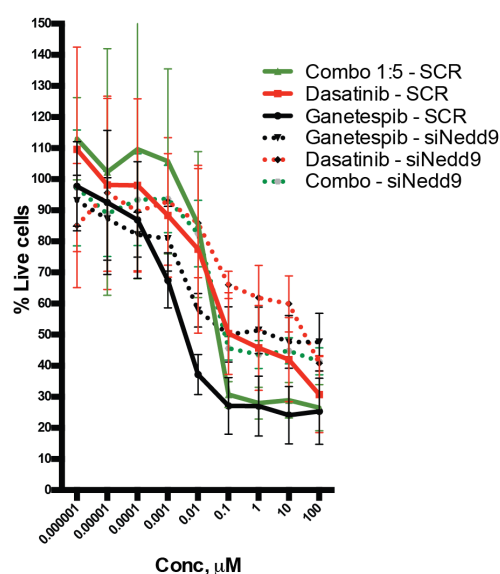


Figure 13. Reduction in cell viability relative to vehicle-treated control following indicated drug treatments, for SCR- or NEDD9-depletion.

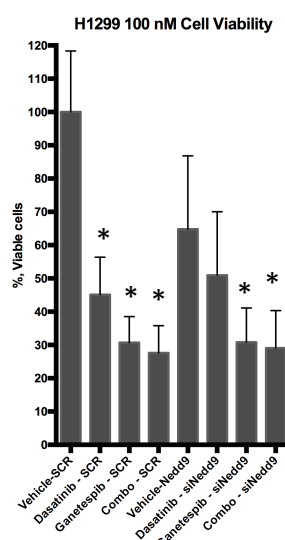


Figure 14. Viability of scrambled control of Nedd9-depleted cells following treatment with the indicated drugs. *, $p < 0.05$ relative to veh/SCR.

Analysis of the H1299 data shown here supported several conclusions: 1) In control cells, treatment with ganetespib was effective in vitro, with an IC₅₀ of 10 nM, and reducing the viability by 70% at 30-50 nM. 2) Dasatinib was less effective in these cells, with an IC₅₀ of 100 nM, and total reduction of

cell growth no more than 60% except at high concentrations where off-target activity was expected. 3) The combination of ganetespib and dasatinib was not more effective than ganetespib. 4) In NEDD9-depleted cells, drugs were less effective. The maximum induction of loss of viability with any drug was 55% relative to starting values, complicating efforts to generate an IC₅₀ value. Specimens are being analyzed by RPPA, but this data is not yet processed and available. Results will be incorporated in the final publication.

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What opportunities for training and professional development has the project provided?

This project provided extensive training and professional development to responsible staff, and other laboratory staff who either assisted or took advantage of the opportunity provided to learn new techniques. Anna Gaponova (in a Ph.D. training program) received extensive training in the analysis of MRI images and performance of xenograft experiments involving assessment of drugs. Ms. Gaponova also provided training to

multiple undergraduates working in the laboratory over the past summer, who shadowed her in the performance of experiment. She communicated these skills to other laboratory staff, including 1 postdoctoral fellow and 1 MD/PhD student. She has worked with the PI of the project to learn how to analyze and present the resulting data in research papers and seminars. Based on these skills and data generated in this project, she successfully defended her doctoral thesis, and received a position at a new institution and a postdoctoral fellow. In the final period of the project, multiple laboratory personnel contributed to the analysis of the RPPA data, providing training to undergraduates and graduate students in the use of statistical techniques to identify significant signaling patterns, and how to validate this data through Western blotting.

How were the results disseminated to communities of interest?

This project resulted in multiple intramural oral presentations over the past year, including presentations to a Translational Research Disease Group focused on identifying translational opportunities for lung cancer research, programmatic meetings of the Molecular Therapeutics program, and submission of an abstract to a Philadelphia-area translational forum. We are currently preparing a manuscript describing the results of the study, which will be submitted in early 2017, and describe the complete results of the project.

What do you plan to do during the next reporting period to accomplish the goals?

Nothing to Report

IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

This project has impact in several distinct areas. First, it informs our basic understanding of NEDD9. Increased NEDD9 expression has been found in many cancers as they become more aggressive, and artificially increased NEDD9 expression generally thought to increase aggressiveness. We have found that absence of NEDD9 can also cause increased aggressiveness and invasion. This was very surprising. Our data suggest that early tumor growth in the absence of NEDD9 selects for changes in tumor biology that eliminate dependence on this central signaling scaffold. This differs from and expands current thinking about the role of this protein in tumor growth and progression. This strongly supports the need to study NEDD9 in the context of a normal tumor microenvironment, which could be clinically important.

Second, our data indicate at least some changes in these tumors are likely to be tumor-intrinsic, and to involve downregulation of activity of the NEDD9 partner SRC, and upregulation of vimentin, in a manner associated with epithelial-mesenchymal transition (EMT) and/or mesenchymal-amoeboid transition (MAT). This is associated with greater sensitivity of tumors that develop in the absence of NEDD9 to SRC inhibitors. This work helps to validate NEDD9 expression as a useful biomarker for use in treatment of lung cancer with agents targeting the SRC pathway. In contrast, our data show that NEDD9 expression has no effect on response to a broadly targeted therapeutic agent, the HSP90 inhibitor ganetespib.

Third, our RPPA data for the first time show that absence of NEDD9 expression causes significant changes in the expression of proteins that function in the processes of autophagy and translational control. This has not previously been reported, and will provide the basis for further investigation.

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

CHANGES/PROBLEMS:**Changes in approach and reasons for change**

Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them

The last piece of the project we are completing is the analysis of the last cell lines to replicate results for Major Task 1. The delay in completing this work was due to the need to invest significant effort in the second year to the analysis of data from Major Task 2 (in vivo experiments), which had been slowed because of recalcitrant breeding of mice needed to generate the cohorts required for analysis, during the first year of the project. This is in progress, and will not take long to complete, but is not yet done at the time of this final report.

Changes that had a significant impact on expenditures

None

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

None

Significant changes in use or care of human subjects

Not applicable, no human subjects

Significant changes in use or care of vertebrate animals.

None

Significant changes in use of biohazards and/or select agents

None

PRODUCTS: Nothing to Report**Publications, conference papers, and presentations**

Nedd9 depletion in murine model promotes more aggressive lung cancer phenotype. Alexander Deneka and Anna Nikonova, *Postdoc Day, Fox Chase Cancer Center, 2016*.

Absence of Nedd9 promotes a more aggressive lung cancer phenotype but sensitizes tumors to dasatinib. *Lung Cancer/Mesothelioma Translational Research Disease Group Meeting, Fox Chase Cancer Center, 2016*.

Constitutive *Nedd9*^{-/-} genotype promotes lung cancer aggressiveness and therapy sensitivity. Deneka, A.Y., Kopp, M., Nikonova, A.S., Gaponova, A.G., Nagele, A., Hensley, H., and Golemis, E.A. *Temple University School of Medicine, Translational Forum October 2017. Poster presented: won first prize.*

Constitutive *Nedd9^{-/-}* genotype promotes lung cancer aggressiveness. Deneka, A.Y., Kopp, M., Nikonova, A.S., Gaponova, A.G., Nagele, A., Hensley, H, Serebriiskii, I., and Golemis, E.A. *Abstract submitted to AACR for 2017 annual meeting.*

A constitutive *Nedd9^{-/-}* genotype promotes invasion and dasatinib sensitivity of non-small cell lung cancer (NSCLC) tumors. Authors, Anna Gaponova, Alexander Y. Deneka, Anna S. Nikonova, Meghan Kopp, Harvey H. Hensley, Ilya G. Serebriiskii, Brian Egleston, and Erica A. Golemis: *Manuscript in preparation, as of December 2016.*

Website(s) or other Internet site(s)

Nothing to Report

Technologies or techniques

Nothing to Report

Inventions, patent applications, and/or licenses

Nothing to Report

Other Products

Nothing to Report

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS:

What individuals have worked on the project?

Name	Project Role	Contribution to Project
Erica Golemis, Ph.D.	Principal Investigator	Overall administration and guidance of the research; Training and management of personnel involved
Anna Gaponova	Graduate Student	In vitro and in vivo experiments proposed; Mouse work
Illya Serebriiskii, Ph.D.	Research Scientist	Data collection and analysis

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period? Not applicable

What other organizations were involved as partners?

Synta Pharmaceuticals, Lexington PA, provided in-kind support (supply of the drug ganetespib)

SPECIAL REPORTING REQUIREMENTS: None

Collaborative Awards: Not applicable

Quad Charts: Not applicable

APPENDICES: Not applicable